and, if said one immunogen is whole cell pertussis, the schedule is one other than a schedule of three doses at one week intervals, all given in the first month,

where, when all of the immunogens administered are selected from the group consisting of BCG, diphtheria, tetanus, whole cell pertussis, polio, hepatitis B, hemophilus influenza, measles, mumps and rubella immunogens, at least one of the following conditions applies: (a) one or more immunogens are administered on at least three different dates prior to 42 days after birth, or (b) one or more immunogens are administered on at least three different dates, and the maximum interval between administrations is at least one day and not more than about two weeks.

REMARKS

We previously filed an amendment after final rejection on February 21, 2002, which was denied entry on June 4, 2002.

In response to the advisory action, we are filing three substitute amendments, of which this is one.

1. In the advisory action, the Examiner said that "amendment of claim 148 to add 'at least one day' would raise the issue of new matter". We strongly disagree.

Claim 148 has been amended in the light of the last paragraph on page 6 of the November 5, 2001 office action:

> The phrase "the maximum interval between administrations is about two weeks or less" in claim 148 renders the claim indefinite, as the lower limit of the claimed range cannot be ascertained.

The Examiner's attention is first respectfully directed to MPEP §2173.05(c)(II), page 2100-149, col. 2:

> In a claim directed to a chemical reaction process, a limitation required that the amount of one ingredient in the reaction mixture should "be maintained at less than 7 mole percent" based on the amount of

> another ingredient. The examiner argued that the claim was indefinite because the limitation sets only a maximum amount and is inclusive of substantially no ingredient resulting in termination of any reaction. The court did not agree because the claim was clearly directed to a reaction process which did not warrant distorting the overall meaning of the claim to preclude performing the claimed process. In re Kirsch, 498 F.2d 1389, 182 USPQ 286 (CCPA 1974).

Hence, the requirement of a lower limit is improper. Nonetheless, in the interest of narrowing the issues for appeal, we have amended claim 148 to supply a lower limit. This lower limit has clear basis.

At page 26, line 28 to page 27, line 3, the specification teaches that the interval can be about 7 days. In Example 2 and 5 the shortest interval was 2 days (page 83, lines 16-17; page 88, line 10). In Example 4, it was 3 days (page 87, lines 9-10).

At page 26, lines 8-11, the specification says:

> For the purpose of the appended claims, the administration of two different immunogens, or of two packets of the same immunogen, within a period of less than 24 hours, is considered a single dosing.

This implies that administrations 24 hours (1 day) apart <u>are</u> permissible and qualify as two separate dosings. Administrations less than 24 hours apart would be considered parts of a single dosing, and the "interval" limitation would not apply. Thus, by definition, the interval between dosings cannot be less than one day.

The foregoing is ample basis for "at least one day".

We previously (August 17, 2001) amended claim 40 to introduce the same limitation. The Examiner "acknowledged" this amendment and did not question that this limitation was proper and overcome the "no lower limit" rejection (November 5, 2001 OA

at page 5, lines 305). We do not understand why the amendment was considered proper in claim 40 and improper here. If there is a problem with the "lower limit" in 148, there is one in 40, too, and prosecution should be reopened to address it (whereupon the substitute "after final" amendments A-C should be entered as of right).

2. Claim 148 is a method claim paralleling kit claim 102. Both claims were presented in view of §4(i) of the May 4, 1999 office action, and both were based on page 29, lines 13-19. Claim 148 has not been rejected on prior art grounds.

3. The Examiner has questioned the definiteness of certain terminology in claim 148. In particular, the examiner questions whether the state of maturation of the immune system (claim 148) is known in the art, or determinable without undue experimentation, for mammals other than mice or rats, or how it is to be correlated to that in a mouse or rat.

Claim 148 is based on page 29, lines 13-19 of the specification:

> The present invention therefore can include administration of the immunogens to humans when said humans immune systems are in a state of maturation and responsiveness comparable to that of mice or rats at the times indicated above, in such circumstances as it would be less effective to administer those immunogens to humans at the same chronological ages as they were administered to mice or rats.

The Examiner says that no markers of maturation are disclosed. This ignores the text at page 27, line 15 to page 29, line 12.

At page 27, lines 15-23, we begin:

> The immune systems of mice and men mature at comparable rates, with both species capable of mounting immune responses to vaccine antigens by the time the recipients are several months old. A comparison of the

> experimental and epidemiological examples in this specification supports this conclusion. Subtle differences in the rates of development of the immune systems of mice and humans may be detected however using a broad range of assays including in vivo assays, in vitro assays, in vitro assays and phenotypic cell assays.

The markers subsequently disclosed include:

(1) antibody titers in blood;

(2) DTH response;

(3) ability of T-cells to divide;

(4) ability of B-cells to divide;

(5) ability of immunocytes to secrete specific lymphokines;

(6) number of lymphocytes in the blood; and

(7) number of macrophages in the blood.

We do not understand why "correlation" should present any difficulties.

4. The Examiner briefly questioned (OA §8) the "description" for claim 148. As previously indicated, it is at page 27, line 15 to page 29, line 19.

5. While claim 148 was rejected for lack of enablement (OA §10), the enablement rejection only addressed claims 145 and 149-152 specifically.

Claim 148 is plainly presented in response to the Examiner's previous attempt to question the extrapolation of data from mice to humans "because of the criticality of the age of administration of the immunogen and the differences in maturation rates between rodents and humans". The Examiner has failed to explain why claim 148 does not overcome the enablement rejection.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The

attached page is captioned "Version with markings to show changes made".

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

Claim 148 has been amended as follows:

148 (amended). A method of reducing the incidence or severity of a chronic immune-mediated disorder in a mammal which comprises administering to said mammal one or more immunogens, according to an immunization schedule by virtue of which the mammal receives, at one or more pharmaceutically acceptable doses of said immunogens, said administrations resulting in an immune response in said mammal which substantially reduces the incidence or severity of at least one chronic immune-mediated disorder in the mammal,

the first dose of said immunization schedule being administered before the mammal's immune system arrives at a state of maturation comparable to that achieved at an age of 42 days after birth in a mouse or rat,

where, if only one immunogen is administered according to said immunization schedule, that immunogen is one other than BCG, and, if said one immunogen is whole cell pertussis, the schedule is one other than a schedule of three doses at one week intervals, all given in the first month,

where, when all of the immunogens administered are selected from the group consisting of BCG, diphtheria, tetanus, whole cell pertussis, polio, hepatitis B, hemophilus influenza, measles, mumps and rubella immunogens, at least one of the following conditions applies: (a) one or more immunogens are administered on at least three different dates prior to 42 days after birth, or (b) one or more immunogens are administered on at least three different dates, and the maximum interval between administrations is <u>at least one day and not more than</u> about two weeks[, or less].